II. REMARKS

Formal matters

Claims 32-36, 38-40, and 42-45 are pending after entry of the amendments set forth herein.

Claims 32-36, 38, 39, and 41 were examined and were rejected. Claims 40 and 42-44 were withdrawn from consideration.

Claim 41 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 32 and 36 are amended. The amendments to claims 32 and 36 were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. Support for the amendments to claims 32 and 36 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: claim 32: page 8, line 17 to page 10, line 7; page 21, lines 6-8; page 22, lines 1-3, 11-13, and 22-23; page 23, lines 11-16; and Figure 4; and claim 36: page 8, line 17 to page 10, line 7; page 21, lines 6-8; page 22, lines 1-3, 11-13, and 22-23; page 23, lines 11-16; Figure 4; and page 19, lines 4-5. Accordingly, no new matter is added by the amendments to claims 32 and 36.

Claim 45 is added. Support for new claim 45 is found in the claims as originally filed, and throughout the specification, including the following exemplary location: page 19, lines 4-5. Accordingly, no new matter is added by new claim 45.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Withdrawn rejections

Applicants note with gratitude that the following rejections, raised in the Office Action mailed May 28, 2008, have been withdrawn:

1) rejection of Claims 40, 42, and 43 under 35 U.S.C. §102(e) as allegedly anticipated by Scholar et al. (US Patent No. 5,552,390); and

2) rejection of Claims 40-43 under 35 U.S.C. §103(a) as allegedly unpatentable over Scholar et al. (US Patent No. 5,552,390) in view of Barsoum et al. (WO 94/046686).

Objection to Claim 32

The Office Action stated that the amendment filed on September 19, 2007 is not in compliance with 37 C.F.R. 1.121 as Claim 32 does not properly amend previous Claim 32. Claim 32 as presented in the amendment of September 19, 2007 has improperly deleted "[Y]" and "[Z]" from the base formula.

Claim 32 has been amended to include "[Y]" and "[Z]" in the base formula. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the objection.

Rejection under 35 U.S.C. §103(a)

Claim 36 was rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Bennett et al. (WO 91/16901; "Bennett") in view of Barsoum et al. (WO 94/04686; "Barsoum").

The Office Action stated that the rejection over Bennett in view of Barsoum was maintained "for reasons of record." It is presumed that the reasons of record are those set out in the May 5, 2006 Office Action. The May 5, 2006 Office Action stated that Bennett teaches a nucleic acid of GGAAGGTTTCCAGGGAAGAGG; that Bennett differs by not conjugating to a peptide; and that Barsoum teaches delivery of cargo molecules, such as nucleic acids, to the cytoplasm and nuclei by use of a transport polypeptide that comprises one or more portions of HIV tat protein which are covalently linked to cargo molecules. The May 5, 2006 Office Action stated that it would have been obvious to conjugate the nucleic acid of Bennett to the transport peptides of Barsoum. Applicants respectfully traverse the rejection.

Applicants' position on this rejection has been made of record, e.g., in the amendment, filed on August 27, 2007 and responsive to the March 26, 2007 Office Action. Applicants respectfully traverse the rejection.

The law regarding obviousness

In order to meet its burden in establishing a rejection under 35 U.S.C. § 103(a), the Patent Office must first demonstrate that the combined prior art references teach or suggest all the claimed limitations.[1] In addition to demonstrating that all elements were known in the prior art, the Patent Office must also articulate a reason for combining the elements.[2] A generalized motivation to develop a method is not the kind of motivation required by

[1] M.P.E.P. § 2143(A).
[2] *See, e.g., KSR Int'l Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007) ("KSR") at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.,* 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*; and *Innogenetics, N.V. v. Abbott Laboratories,* 512 F.3d 1363,

the patent laws.[3]

In *KSR*, the Supreme Court reviewed the teaching-suggestion-motivation (TSM) test. While the Court warned against its rigid application,[4] the Court also found that the TSM test could provide a "helpful insight" in determining whether the claimed subject matter is obvious under § 103(a).[5] The Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis."[6] Indeed, in *KSR*, the Court stated that the "Graham" factors[7] still control an obviousness inquiry. The Graham factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness.[8] Subsequently, the Federal Circuit reiterated the value of the TSM test, stating that a flexible TSM test remains the "primary guarantor against a non-statutory hindsight analysis."[9]

The Court in *KSR* repeatedly emphasized that an obviousness inquiry must take into account the predictability of the field:[10]

> the same field or a different one. If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative—a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

(emphasis added)

In *Eisai v. Reddy*,[11] Federal Circuit noted that the Supreme Court's analysis in *KSR* relies on several

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1373, 85 USPQ2d 1641 (Fed. Cir. 2008).
[3] *Innogenetics, N.V. v. Abbott Laboratories,* 512 F.3d 1363, 1373, 85 USPQ2d 1641 (Fed. Cir. 2008).
[4] *KSR Int'l Co.,* at 1741.
[5] *Id. See also*, Memorandum to Technology Directors from Margaret A. Focarino, Deputy Commissioner for Patent Operations, May 3, 2007.
[6] *KSR Int'l Co.,* 127 S. Ct. at 1741.
[7] *Graham v. John Deere Co. of Kansas City,* 383 U.S. 1, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966).
[8] *KSR Int'l Co.,* 127 S. Ct. at 1734 (quoting *Graham, 383 U.S. at 17-18*).
[9] *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc.,* 520 F.3d 1358, 1364, 86 USPQ2d 1996 (Fed. Cir. 2008).
[10] *KSR Int'l Co.,* 127 S. Ct. at 1740 (citations omitted).
[11] *Eisai Co. Ltd. and Eisai, Inc. v. Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc. and Teva Pharmaceuticals USA, Inc.*, 2008 U.S. App. LEXIS 15399 (Fed. Cir. 2008).

assumptions about the prior art landscape. These assumptions included: 1) a starting reference point or points in the art, prior to the time of invention, from which a skilled artisan might identify a problem and pursue potential solutions; 2) the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications; and 3) the record before the time of invention would supply some reasons for narrowing the prior art universe to a finite number of identified, predictable solutions. Such assumptions, while possibly relevant to mechanical devices such as were considered in *KSR*, may not be applicable to fields such as the chemical and biological arts.

When considering the Federal Circuit's application of the "obvious to try" standard to the adjustable gas pedal invention at issue, the Court stated:[12]

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.

(emphasis added)

The Supreme Court in *KSR* stated that "a court *must* ask whether the improvement is more than predictable use of prior art elements according to their established functions."[13] The Court in *KSR* cited *Sakraida v. AG Pro*.[14] In *Sakraida v. AG Pro, Inc.*, the Court derived from the precedents the conclusion that when a patent "simply arranges old elements with each performing the same function it had been known to perform" and yields no more than one would expect from such an arrangement, the combination is obvious.[15]

Evidence that supports a finding of non-obviousness includes teaching away, unexpected results, skepticism of others in the field, copying, long-felt but unsolved need, and commercial success.[16] Such evidence must be considered before a conclusion of obviousness is reached.[17] Such evidence is not just a cumulative or confirmatory part of the obviousness calculus, but constitutes independent evidence of non-obviousness,[18] or, as

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[12] *KSR Int'l Co.,* 127 S. Ct. at 1742.
[13] *Id.* at 1740; (emphasis added).
[14] *Sakraida v. AG Pro, Inc.,* 425 U.S. 273, 96 S. Ct. 1532, 47 L. Ed. 2d 784 (1976).
[15] *Id.* at 282.
[16] *Graham,* 383 U.S. at 17 (1996).
[17] *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986).
[18] *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc.,* 520 F.3d 1358, 1365, 86 USPQ2d 1996 (Fed. Cir. 2008).

stated in *Hybritech*, consideration of such evidence is not merely "icing on the cake."[19]

The cited art does not render claim 36 obvious.

Bennett, alone or in combination with Barsoum, neither teaches nor suggests a composition comprising a nucleic acid comprising a hexameric nucleotide sequence AAGGTT, wherein the nucleic acid is 6 nucleotides to 45 nucleotides in length, and wherein the nucleic acid is conjugated to a peptide, as recited in claim 36.

Bennett discusses **antisense oligonucleotides**. Bennett describes introducing antisense oligonucleotides into cells in medium alone or in medium containing DOTMA. Bennett, pages 30, 34, and 35; and Examples 1, 5, and 6. Bennett states that various antisense oligonucleotides reduced levels of 5-lipoxygenase significantly. Bennett, page 33, lines 32-35. There is no discussion in Bennett of difficulty in getting the antisense oligonucleotides into cells. As the May 5, 2006 Office Action acknowledged, Bennett does not disclose a nucleic acid conjugated to a cargo peptide.

Barsoum discusses use of a Tat polypeptide for cytoplasmic and nuclear delivery of biologically active non-tat proteins, nucleic acids and other molecules **that are not inherently capable of entering target cells or cell nuclei**, or **are not inherently capable of entering target cells at a useful rate**. Barsoum, page 5, lines 13-20. Bennett does not characterize the antisense oligonucleotides discussed therein as "not inherently capable of entering target cells or cell nuclei," or "not inherently capable of entering target cells at a useful rate." As such, there would be no motivation in the cited references to combine the reference teachings.

Barsoum neither discloses nor suggest conjugating a nucleic acid to a peptide. As such, the combination of Bennett and Barsoum does not disclose or suggest all of claim elements as recited in claim 36. As such, Bennett, alone or in combination with Barsoum, cannot render claim 36 obvious.

Furthermore, Bennett does not disclose or suggest a nucleic acid as recited in claim 36, wherein the nucleic acid reduces the level of one or more of IFNβ, IFNα, IL-12, IFN-γ, and IL-18. There is no discussion of any such activity in Bennett. Such a property would not have been expected from Bennett.

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[19] *Hybritech,* 802 F.2d at 1380.

As noted above, evidence of non-obviousness, such as unexpected properties, must be considered before a conclusion of obviousness is reached.[20] Barsoum does not cure the deficiency of Bennett. Barsoum merely discusses use of a Tat polypeptide for cytoplasmic and nuclear delivery of biologically active non-tat proteins. As such, Bennett, alone or in combination with Barsoum, cannot render claim 36 obvious.

Nevertheless, and solely in the interest of expediting prosecution, claim 36 is amended to recite that the peptide to which the nucleic acid is conjugated is a targeting peptide, and that the nucleic acid reduces the level of one or more of IFNβ, IFNα, IL-12, IFN-γ, and IL-18.

Conclusion as to the rejection under 35 U.S.C. §103(a)

Applicants submit that the rejection of claim 36 under 35 U.S.C. 103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejections under 35 U.S.C. §112, first paragraph

Claims 32-35, 38, 39, and 41 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Claim 41 was rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Enablement

The Office Action states "the specification teaches that the immune inhibitory oligodeoxynucleotides (IIS-ODN) autoantigen conjugates are useful in boosting host Th2 type immune response to the autoantigen (suppressing the Th1 responses by the autoantigen itself) and the ISS-ODN autoantibody conjugate are useful in inducing passive immunity in a host suffering from an autoimmune condition." The Office Action further states "[t]he alleged switch from a Th1 to a Th2 response by the IIS-ODN autoantigen conjugate is not enabled to treat or prevent any autoimmune disease or specific diseases contemplated in the specification." Applicants respectfully traverse the rejection.

It is incumbent upon the Patent and Trademark Office to explain why it doubts the truth or

[20] *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986).

accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The Office Action has not presented convincing scientific rationale.

The instant specification provides ample description as to how to make and use a claimed composition.

The instant specification provides ample description as to how to make and use an IIS.

The instant specification states that IIS reduce the immunostimulatory effect of ISS. The Specification, page 7, lines 4-11 states:

> The IIS-ON of the invention reduce the immunostimulatory effect of ISS-ODN. Structurally, ISS-ODN are non-coding oligonucleotides 6 mer or greater in length which may include at least one unmethylated CG motif. The relative position of each CG sequence in ISS-ODN with immunostimulatory activity in certain mammalian species (e.g., rodents) is 5'-CG-3' (i.e., the C is in the 5' position with respect to the G in the 3' position). Many known ISS-ODN flank the CG motif with at least two purine nucleotides (e.g., GA or AA) and at least two pyrimidine nucleotides (e.g., TC or TT) to enhance the B lymphocyte stimulatory activity of the immunostimulatory polynucleotide (see, e.g., Krieg, et al, Nature, 374:546-549, 1995).

The instant specification also notes that ISS have been implicated in the onset and exacerbation of autoimmune disease. Specification, page 7, lines 22-24 states:

> Interestingly, a CpG containing oligonucleotide comparable to bacterial ISS-ODN has also recently been implicated in the onset and exacerbation of autoimmune disease through an IL-12 dependent pathway (Segal, et al, J. Immunol., 158:5087 (1997)).

The instant specification states that IIS reduce the level of one or more of IFNβ, IFNα, IL-12, IFN-γ, and IL-18, e.g., in the context of treating autoimmune disorders. Specification, page 21, lines 6-8; page 22, lines 1-3, 11-13, 22, and 23; and page 23, lines 11-16. Furthermore, the instant specification teaches how to determine whether an IIS will reduce the level of one or more of IFNβ, IFNα, IL-12, IFN-γ, and IL-18. Specification, page 8, line 17 to page 9, line 7.

The instant specification provides ample description of IIS. Specification, page 10, line 8 to page 13, line 11. The instant specification describes how to determine whether a given nucleic acid reduces

the immunostimulatory effect of an ISS, and thus exhibits immunoinhibitory activity. Specification, page 8, line 17 to page 9, line 13; and Examples I-III.

The instant specification states that an IIS can be conjugated to an autoantigen or an autoantibody. Specification, page 18, lines 9-14; and page 18, line 14 to page 19, line 2. The specification describes various conjugation methods, a number of which were known in the art as of the priority date of the instant application. Specification, page 19, line 19 to page 20, line 2.

Finally, the instant specification provides ample description of how to administer an IIS or an IIS conjugate. Specification, page 21, line 1 to page 24, line 22. The instant specification provides a description of how to determine whether a Th2-type immune response has been induced. Specification, page 21, lines 11-16.

The instant specification provides working examples of the immunoinhibitory effect of a subject immunoinhibitory nucleic acid.

For example, Example I shows *in vitro* inhibition of ISS-stimulated proliferation of mouse splenocytes, by contacting ISS-stimulated splenocytes with IIS. Example II shows *in vitro* inhibition of ISS-stimulated production of IFN-γ by mouse splenocytes, by contacting ISS-stimulated splenocytes with IIS.

Example III shows *in vivo* induction of a Th2 immune response in mice. Mice were primed with the model antigen β-galactosidase (β-Gal) plus either an IIS or an ISS. Mice were subsequently challenged with β-Gal, and indicators of Th1 (e.g., IgG2a) and Th2 (e.g., IgE; IgG1) were measured. As shown in Figure 5, priming with IIS and β-Gal resulted in production of higher levels IgE when mice were challenged with β-Gal, compared to IgE levels produced by mice primed with ISS and β-Gal and challenged with β-Gal. In addition, as discussed in Example III, high levels of IgG2a antibodies (indicators of a Th1-type immune response) and low levels of IgG1 (indicators of a Th2-type immune response) were induced in response to β-Gal challenge in (ISS + β-Gal)-primed mice, while the low levels of IgG2a antibodies and high levels of IgG1 antibodies were induced in response to β-Gal challenge in (IIS + β-Gal)-primed mice.

Thus, the working examples provide both *in vitro* and *in vivo* evidence of the effect of IIS on inducing a Th2-type immune response.

Those skilled in the art would reasonably expect that an IIS conjugate would be at least as effective as an IIS in inducing a Th2-type immune response.

As noted above, the instant specification provides ample evidence that an IIS induces a Th2-type immune response *in vivo*. Those skilled in the art would reasonable expect that an IIS conjugate would be at least as effective as an IIS in inducing a Th2-type immune response.

The specification describes *in vivo* effects of ISS in inducing a Th1-type immune response. Specification, page 21, lines 11-12; and page 7, lines 12-14. It has been shown that ISS conjugated to an antigen elicits a more potent Th1 response to the antigen, compared to ISS administered alone or in admixture with the antigen. See, e.g., Cho et al. (2000) *Nat. Biotechnol.* 18:509-514; "Cho"; a copy of was previously provided. There is no reason to believe that an IIS, when conjugated to an autoantigen or autoantibody, would not be effective in inducing a Th2-type immune response.

The Office Action has not provided sufficient scientific rationale as to why one of ordinary skill in the art would not be able to make and use the invention as claimed.

1) The Office Action stated that the "the example [Example 3] does not establish inhibition of the immune response." Office Action, page 5.

However, as noted above, the instant specification provides working examples of the immunoinhibitory effect of a subject IIS. As discussed above, evidence was provided that an IIS induces a Th2-type immune response *in vivo*, as evidenced by production of IgE antibodies and IgG1 antibodies, which are hallmarks of a Th2-type immune response.

Furthermore, one aspect of an IIS conjugate as claimed is that it is capable of inducing a Th2-type immune response in an individual. Applicants showed that an IIS induces a Th2-type immune response *in vivo*. There is no reason to believe that an IIS conjugate would not induce a Th2-type immune response. In fact, as noted above, there are ample scientific reasons why an IIS conjugate would induce a Th2-type immune response.

2) The Office Action stated that "the art does not recognize that generation of a Th2 type immune response is effective to treat autoimmune disease." Office Action, page 5.

However, the art does in fact recognize that generation of a Th2 type immune response is effective to treat autoimmune disease. The following references are illustrative.

a) **Young et al. (2000) *J. Immunol.* 164:3563; "Young"**

Young discusses the effect of Th2 cytokines in inhibition of experimental autoimmune encephalitis (EAE) in an animal model of multiple sclerosis (MS). Young states that EAE is induced in mice by adoptive transfer of activated proteolipid protein peptide (PLP) 139-151-specific Th1 cells. Young, page 3562, column 1, first paragraph. Young further states that T cells responding to altered peptide ligands (APL) of PLP, previously shown to induce Th2 differentiation and regulate disease in PLP-immunized mice, do not transfer EAE. Young presents data showing that Th2 cytokines can effectively down-regulate the encephalitogenic potential of PLP-spleen cells. Young concludes that induction of Th2 cytokines could be of potential therapeutic benefit in the treatment of disease mediated by autoimmune encephalitogenic T cells. Young, page 3571, column 2, third paragraph.

b) **Ho et al. (2003) *J. Immunol.* 171:4920; "Ho 2003"**

Ho 2003 (a copy of which was previously provided) discusses the use of an immunomodulatory GpG oligonucleotide in ameliorating autoimmune disease in an experimental autoimmune encephalitis (EAE) mouse model of multiple sclerosis (MS). Ho 2003states that EAE is a Th1-mediated animal disease model of MS. Ho 2003, page 4920, column 2, second full paragraph. Ho 2003states that the immunomodulatory GpG motif-containing oligonucleotide (IMO) stimulates the proliferation of Th2 cells. Ho 2003, page 4920, column 2, third full paragraph. Ho 2003 demonstrated that the IMO suppressed autoantigen-mediated EAE. Ho 2003, Figure 7; and page 4924, column 1, paragraph 1, to page 4925, column 2, paragraph 1.

Thus, Ho 2003provides further evidence for the fact that an IIS has activity in shifting an immune response from a Th1-type response to a Th2-type response; and is thus useful in treating disorders associated with a Th1 response, e.g., an autoimmune disorder.

c) **Ho et al. (2005) *J. Immunol.* 175:6226; "Ho 2005"**

Ho 2005 (a copy of which was previously provided) discusses the use of a mixture of autoantigen and an immunomodulatory GpG oligonucleotide ("GpG ODN") to ameliorate autoimmune

disease in an EAE mouse model of MS. Ho 2005 states that the immunomodulatory GpG-ODN counteracted the CpG-induced inflammatory effect in a Th1-mediated autoimmune disease by skewing both the autoaggressive T cell and B cell responses toward a protective Th2 phenotype. Ho 2005, Abstract.

Ho 2005 provides data showing that a combination of GpG ODN (IIS) and autoantigen shifted an immune response toward a Th2-type immune response, and resulted in amelioration of an autoimmune disorder. Those skilled in the art would reasonably expect that, as disclosed in the instant specification, an autoantigen-IIS conjugate would also shift an immune response toward a Th2-type immune response; and would therefore be useful in an autoimmune disease.

d) **Shirota et al. (2004) *J. Immunol.* 173:5002; "Shirota"**

Shirota states that suppressive oligodeoxynucleotides (ODN) can suppress Th1-mediated immune responses. Shirota, page 173, column 1, paragraph 2. Shirota states that a suppressive ODN was proven effective in the prevention/treatment of certain Th1-dependent autoimmune diseases. Shirota, Abstract. Shirota states that the study was undertaken to elucidate the mechanism whereby suppressive ODN would be effective in treating autoimmune disease. Shirota states that the findings "indicate that suppressive ODN selectively reduce Th1 cytokine production, while enhancing Th2 immunity." Shirota, page 173, column 2, first paragraph.

e) **Dong et al. (2004) *Arthritis Rheum.* 50:1686; "Dong 2004"**

Dong 2004 reports on the use of suppressive oligonucleotides (ODNs) to treat collagen-induced arthritis (CIA), a murine model of rheumatoid arthritis (RA), an autoimmune disease. Dong 2004 states that suppressive ODNs can inhibit the immune activation and arthritis induced by CpG motifs. Dong 2004, page 1686, column 2, first paragraph. Dong 2004 states that suppressive ODNs administered during the inductive phase of CIA significantly reduced the incidence and severity of arthritis. Dong 2004 states that treatment with suppressive ODNS significantly decreases serum titers of pathogenic IgG anti-CII autoantibodies and IFN-γ production by collagen-reactive T cells. Dong 2004 concludes that suppressive ODNs may be of therapeutic value in the treatment of RA, and potentially other autoimmune diseases." Dong 2004, page 1686, column 1, fourth paragraph. According to Shirota (above), the suppressive ODN induce a Th2-type immune response.

f) **Dong et al. (2005) *Arthritis Rheum.* 52:651; "Dong 2005"**

Dong 2005 describes the use of suppressive oligodeoxynucleotides (ODNs) for the treatment of autoimmune disease in an animal model of systemic lupus erythematosus (SLE). Dong 2005 states that suppressive ODN significantly prolonged lifespan and delayed onset and progression of glomerulonephritis in the SLE mouse model. Dong 2005 concludes that suppressive ODN may e of benefit in the treatment of chronic systemic autoimmune diseases such as SLE. According to Shirota (above), the suppressive ODN induce a Th2-type immune response.

g) **Zeuner et al. (2002) *Arthritis and Rheum.* 46:2219; "Zeuner"**

Zeuner describes the effect of suppressive oligodeoxynucleotides (ODNs) on CpG (ISS)-induced arthritis in an animal model. Zeuner states that administration of suppressive ODN reduced the manifestations and severity of arthritis up to 80%. Zeuner, page 2219, column 1, paragraph 4. According to Shirota (above), the suppressive ODN induce a Th2-type immune response.

h) **Gaupp et al. (2008) *Am. J. Pathol.* 173:119; "Gaupp"**

Gaupp presents data showing that, in an experimental autoimmune encephalitis (EAE) animal model of multiple sclerosis, amelioration of encephalitis correlated with an up-regulation of Th2-type cytokines.

i) **Cheng et al. (2008) *J. Mol. Cell Cardiol.* 45:168; "Cheng"**

Cheng states that suppressive oligonucleotides selectively reduce Th1 cytokine production, and have been proven effective at blocking the development of organ-specific autoimmune diseases.

j) **Jin et al. (2008) *J. Immunol.* 180:58; "Jin"**

Jin describes a peptide, P277, that, when tandemly repeated, enhances a Th2 immune response in an animal model of type 1 (autoimmune) diabetes.

k) **Ramshaw et al. (Aug., 1997) *Immunol. Cell Biol.* 75:409; "Ramshaw"**

Ramshaw discusses use of DNA vaccines for treating autoimmune disorders. Ramshaw notes that Th1 cells appear to be involved in many organ-specific autoimmune diseases, and that suppression of disease is associated with the Th2 phenotype. Ramshaw states that the induction of a Th2 response might be expected to have an effect on the course of autoimmune disease. Ramshaw provides data

showing that DNA immunization induced a Th2 response and protected animals against EAE, a model of multiple sclerosis.

Those skilled in the art would find it reasonable to expect that an IIS-autoantigen conjugate would induce a Th2-type immune response.

As noted above, a subject IIS induces a Th2-type immune response. Also as noted above, those skilled in the art would find it reasonable to expect that inducing a shift away from a Th1 response and toward a Th2 response would be effective in treating an autoimmune disorder. Furthermore, as discussed previously, just as an ISS-allergen conjugate is efficacious in inducing a Th1-type immune response (thereby reducing an allergic response to the allergen), an IIS-autoantigen conjugate would induce a Th2-type immune response to an autoantigen. As such, those skilled in the art would find it reasonable to expect that an IIS-autoantigen conjugate would induce a Th2-type immune response, and would be effective in treating an autoimmune disease.

The art cited in the Office Action does not lead to a conclusion of lack of enablement.

The Office Action cited various references; and stated that the art teaches that a Th1-Th2 cytokine switch or presence is not correlative of a therapeutic response. Applicants respectfully traverse.

As discussed previously, the art cited in the Office Action does not lead to a conclusion that instant claims 32-35, 38, 39, and 44 lack enablement.

The Office Action cited Louzoun et al. ((2001) *J. Autoimmunity* 17:311-321; "Louzon"); Brunet et al. ((2002) *Trends Immunol.* 23:127-128; "Brunet"); Genain et al. ((1996) *Science* 274:2054; "Genain"); and Hofstetter et al. ((2002) *J. Immunol.* 169:117-125; "Hofstetter").

Louzon

The Office Action stated that many investigators consider the Th1/Th2 paradigm an overly simplistic way to view highly complex systems; and cited Louzon.

Louzon presents a model that is stated to explain both the general agreement and the apparently contradictory results described by various groups. Louzon actually supports the Th1/Th2 paradigm. As such, Louzon does not lead to a conclusion that claims 32-35, 38, 39, and 44 lack enablement.

Brunet

The Office Action stated that therapeutic manipulation of the Th1-Th2 balance is inherently dangerous and unpredictable; and cited Brunet.

However, Brunet does not discuss use of an IIS-autoantigen or IIS-autoantibody conjugate. As such, Brunet is not relevant to a determination of enablement of any of claims 32-35, 38, 39, and 44.

Furthermore, safety is not within the purview of the U.S. Patent Office; instead, safety considerations are within the purview of the U.S. Food and Drug Administration.

Genain

The Office Action stated that Genain teaches that immune deviation and shift of a cytokine production from a Th1 pattern to a Th2 pattern increased titers of autoantibodies, increase pathogenic autoantibodies and exacerbate autoimmune disease.

However, Genain discusses administration of myelin oligodendrocyte glycoprotein (MOG), which is said to be a minor constituent of myelin, to an experimental animal model of multiple sclerosis. Genain does not discuss use of an IIS-autoantigen conjugate. As such, Genain is not relevant to a determination of enablement of any of claims 32-35, 38, 39, and 44.

Hofstetter

The Office Action stated that the art teaches that autoimmune Th1 responses can develop and continue even in the presence and high frequencies of Th2 cells; and cited Hofstetter.

Hofstetter discusses administration of pertussis toxin (PT) to an experimental autoimmune encephalomyelitis (EAE) mouse, an experimental animal model of multiple sclerosis (MS). Hofstetter states that administration of PT to the EAE mouse prevented the protection from EAE conferred by injection of a peptide that induced a Th2 response. The purpose of the study was to assess the various effects of PT on the pathogenicity, cytokine differentiation, and clonal sizes of neuroantigen-reactive T cells in EAE in mice. Hofstetter does not conclude that inducing a Th2 response is not helpful in treating an autoimmune disorder. Hofstetter merely analyzed the effect of PT on the protection conferred by injection of neuroantigens. As such, Hofstetter does not lead to a conclusion that claims 32-35, 38, 39, and 44 lack enablement.

Hofstetter does not discuss use of an IIS-autoantigen conjugate. As such, Hofstetter is not relevant to a determination of enablement of any of claims 32-35, 38, 39, and 44.

Post-priority date references support the fact that claims 32-35, 38, 39, and 44 are enabled.

Others in the field recognize the usefulness of IIS in shifting an immune response from a Th1-type response to a Th2-type response; and recognize the usefulness of such a shift in, e.g., the treatment of autoimmune disorders.

As previously described, Ho 2003 and Ho 2005 provide further evidence for the fact that an IIS has activity in shifting an immune response from a Th1-type response to a Th2-type response; and is thus useful in treating disorders associated with a Th1 response, e.g., an autoimmune disorder.

In addition, Dong 2004, Dong 2005, Shirota, and Zeuner, described in detail above, provide further evidence for the fact that an IIS has activity in shifting an immune response from a Th1-type response to a Th2-type response; and is thus useful in treating disorders associated with a Th1 response, e.g., an autoimmune disorder.

The Office Action stated that "developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing." Office Action, page 7. However, it is well established that post-filing references can provide evidence of enablement, e.g., where the post-filing references describe successful carrying out of a method described in a patent application, or successful use of a composition described in a patent application.

Written description

Claim 41 is cancelled without prejudice to renewal, thereby rendering this rejection of claim 41 moot.

Conclusion as to the rejections under 35 U.S.C. §112, first paragraph

Applicants submit that the rejections of the claims discussed above 5 U.S.C. §112, first paragraph, have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejections.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCSD-173CON.

Respectfully submitted,
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Date: 11/26/2008

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